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Pharmacogenomics and Personalized Medicine in Neuropsychiatry

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Despite the need for more effective treatments for psychiatric disorders, development of new medications has stalled. Here we discuss the promise of personalized medicine in developing more efficacious and individualized pharmacotherapies that take into account genetic variation and target groups of patients who share biology, not just symptoms.

Introduction: Pharmacogenomics, Pharmacogenetics, and "Personalized Medicine"

Medication development for mental disorders has stalled over the past three decades. After the serendipitous discovery of antipsychotic and antidepressant medications in the 1950s and 1960s, and the development of more selective and better tolerated compounds in the 1970s and 1980s, the field has come to rely on "me-too" compounds and aggressive marketing. This approach has led to robust sales of medication but little evidence of greater efficacy. One exception is the development of clozapine, an antipsychotic that appears more effective than other compounds but is underprescribed because of rare adverse hematologic events. Recently, many major pharmaceutical companies have all but abandoned drug discovery efforts for mental illness. We may have left behind the era of blockbuster drugs designed to treat large segments of the population. We now need to identify new drug targets and refocus our drug discovery efforts to search—as Munos (2009) put it—for breakthroughs rather than blockbusters.

The need for better treatments is undeniable. Mental illness is now the leading cause of healthy life lost in the developed world and is rising rapidly in developing countries (WHO, 2006; http://www.who.int/mental_health/management/depression/definition/en). Existing antipsychotics fail to address the cognitive symptoms of schizophrenia, such as executive dysfunction, which have been increasingly recognized as highly disabling (Hyman and Fenton, 2003). Available antidepressants act slowly and still fail to bring about remission in more than half of patients with depression. Lithium remains highly effective for some people with bipolar disorder, but most do not enjoy sufficient benefit from lithium or a range of more recently developed mood stabilizers. Posttraumatic stress disorder (PTSD) and other combat-related mental illnesses have reached crisis levels among recent veterans, and yet no medication has proven effective. Suicide, usually related to mental illness, is a major cause of death, with a rate that is now twice the homicide rate and even surpasses traffic fatalities in the U.S. (Centers for Disease Control; http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_04.pdf).

The key lesson of the past decade of clinical trials is the heterogeneity of psychiatric diagnoses. Diagnostic categories, such as schizophrenia, depression, or autism, though each defined by a broader set of observed symptoms, may individually comprise different biological entities with distinct pathophysiologies, requiring different treatments. What we need now are medications for targeted subgroups of patients within diagnostic categories who share biology, not just symptoms. This is the essence of personalized medicine or what has recently been called "precision medicine" (Committee on a Framework for Developing a New Taxonomy of Disease, 2011). Personalized medicine overlaps (Figure 1) with what is coming to be known as "genomic medicine," which uses information from a patient's genome for diagnosis, prognosis, and treatment planning, emphasizing uncommon or unique aspects of each patient (for review, see Feero et al., 2010). Emphasis on the unique aspects of a patient is, in fact, nothing new for psychiatry. Effective psychiatric care has always been challenging, in part, precisely because it has always been personalized. Every unhappy family may indeed be unhappy in its own way. That is why we need a much larger variety of treatments, each with a much narrower range of indications.

Some Pharmacogenomic "Home Runs"

Traditional pharmacogenetics and genomics are forerunners of genomic medicine that use genetic methods to better match patients with treatments. The focus is on genetic markers that correlate with treatment response or adverse events. Unlike clinical trials, which emphasize homogeneity of outcomes, pharmacogenetic studies emphasize heterogeneity. As such, the goal is to maximize efficacy while minimizing adverse events. Genetic variation can affect how individuals handle medications in a variety of ways, ranging from absorption to toxicity, all in the context of other individual variables, such as treatment adherence (Figure 2). Despite this complexity, several pharmacogenetic success stories have emerged in recent years. A few are highlighted here to illustrate how genetics can help to reduce toxicity and adverse events—traditional aims of pharmacogenomics—but also help to identify subgroups of patients with distinct pathophysiology that may be uniquely responsive to particular medications.

Warfarin Dosing Polymorphisms

A set of common genetic variants accounts for up to 40% of the variance in optimal dosage of warfarin, a common anticoagulant (for review, see Carlquist and Anderson, 2011). This discovery has garnered much attention, because bleeding complications from warfarin are not rare and can be serious. In 2010, the FDA revised warfarin labeling to include dosage guidelines based on genotype—a first. However, it is not yet clear that the genetic tests bring additional clinical utility beyond what can be done by skillful monitoring of standard blood clotting assays, such as the INR.

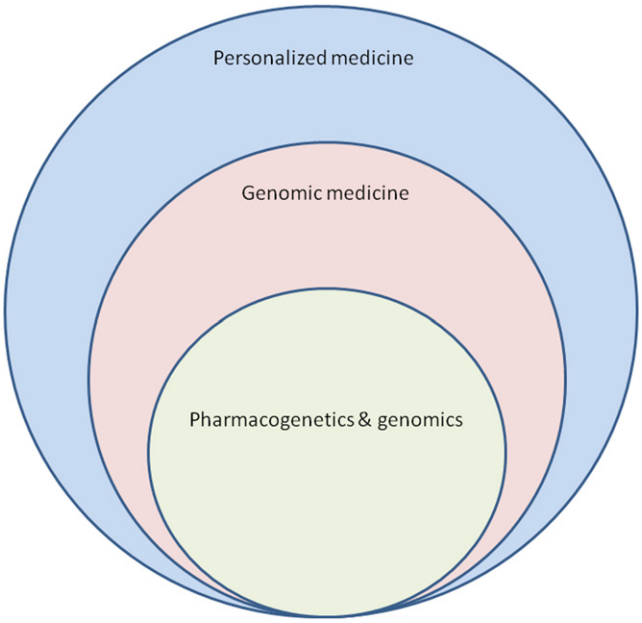

Figure 1. The Nested Relationship between Personalized Medicine, Genomic Medicine, and Pharmacogenetics and Genomics

HLA Marker of Stevens Johnson Syndrome with Carbamazepine

Stevens Johnson syndrome (SJS) is a rare but serious inflammatory disorder of the skin that occurs in a variety of settings but has long been associated with exposure to anticonvulsants such as lamotrigine, carbamazepine, and phenytoin. In 2004, Chung et al. (2004) reported that patients of Han Chinese ancestry who developed SJS after exposure to carbamazepine were substantially more likely to carry the human leukocyte antigen (HLA) haplotype HLA-B*1502, which is common in persons of Asian ancestry. This finding has been confirmed in other Asian populations, but not in non-Asians, in whom HLA-B*1502 is rare.

Recently, the U.S. Food and Drug Administration changed the carbamazepine labeling to highlight the potential value of HLA testing in patients of Asian ancestry being considered for carbamazepine treatment. This is an example of a strong genetic marker for a rare but serious adverse event. The clinical utility in patients of Asian ancestry seems clear, although it is not yet clear whether HLA-B*1502 screening is being widely adopted into clinical practice.

Ivacaftor Treatment for Uncommon Form of Cystic Fibrosis

Cystic fibrosis (CF) was one of the first diseases whose causative gene, CFTR, was identified by human genetic mapping. Subsequent work over two decades revealed that each of the disease mutations in CFTR affects the protein differently, making corrective therapy very challenging. A small-molecule screening approach identified a compound that partially corrected the defect caused by the G551D mutation, present in about 4% of patients with CF. A version of this compound, known as ivacaftor, was later shown to improve health and lung function in patients over 5 years of age who received the drug over 48 weeks (Ramsey et al., 2011). Ivacaftor has not yet been shown to affect survival in G551D carriers and apparently has no benefit for the majority of CF patients, who carry other mutations. Despite these limitations, ivacaftor is one of the first examples of an effective treatment that targets patients carrying a particular disease mutation.

How Can This Work in Neuropsychiatry?

Pharmacogenomic studies have been underway for several years in neuropsychiatry, yet the field still seems in its infancy. Many early studies suffered from a lack of large study cohorts and high-throughput molecular technology, which only became available relatively recently. More recent studies have generated promising leads, but effect sizes remain small and replication studies in large samples are generally lacking.

Cytochrome P450

Most drugs are at least partly metabolized by the cytochrome P450 (CYP) system, a family of enzymes that seems to have evolved to help cope with environmental toxins. Variation in the genes encoding the cytochrome enzymes is extensive and has long been known to affect metabolism of certain drugs, including psychotropics like olanzepine, sertraline, and several benzodiazepines. For these reasons, the CYP genes have been extensively studied in psychiatry and a gene chip that captures most of the relevant functional variation is being promoted for use in the field (for review, see Black et al., 2007). So far, however, the clinical utility of such testing has not been proven for most patients (Evaluation of Genomic Applications in Practice and Prevention [EGAPP] Working Group, 2007).

Candidate Gene and Genome-wide Association Studies of Antidepressant Outcome

Several candidate gene association studies have been carried out in recent years and have identified some promising markers of antidepressant outcome. Numerous studies have implicated SLC6A4 variation in antidepressant treatment outcome, although the outcome phenotypes have varied substantially and a recent meta-analysis found no overall effect (Taylor et al., 2010). Other promising leads include the following: FKBP5, which encodes a protein involved in glucocorticoid trafficking (Binder et al., 2004); HTR2A, which encodes the serotonin 2A receptor (McMahon et al., 2006); and ABCB1, which encodes a p-glycoprotein that affects brain concentrations of some antidepressants (Uhr et al., 2008). All of these findings await robust replication in large samples.

Identification of Treatment-Responsive Subgroups

Most of the common neuropsychiatric disorders probably represent a collection of less common—even rare—diseases. We need to begin to think in terms of "lithium-responsive mood disorder" or "clozapine-responsive psychotic disorder." Such treatment-responsive subgroups may share specific genes or other characteristics. Each of the current diagnostic categories may actually encompass several subgroups for which a new treatment needs to be designed, as underscored by the example of ivacaftor in CFTR therapy summarized above. Autism, which is likely a polygenic disorder, may serve as a good model in developing treatment strategies in the broader realm of neuropsychiatry. Recent work has identified several genomic anomalies associated with autism (reviewed in Malhotra and Sebat, 2012). Each genetic alteration may therefore implicate a distinct molecular etiology, and hence a different potentially "druggable" molecular target. Depending on the underlying molecular or neural substrates, which may differ even within the same diagnostic classification, effective treatment may require cognitive or behavioral treatments rather than medications. Most may require both.

Identification of Patients at High Risk for Severe Adverse Events

As exemplified by SJS during carbamazepine treatment, we need to identify good predictive markers of severe adverse events arising during psychopharmacologic treatment. Such markers could enable much wider use of drugs such as clozapine that offer distinct advantages to the majority of patients, while preventing exposure of those at high risk for severe events. Recent suggestive data on genomic predictors of metabolic syndrome may be an early example of this approach (reviewed in Chowdhury et al., 2011).

Key Challenges

Discovery requires large patient groups. The large number of hypotheses tested in a typical genome-wide experiment poses a substantial multiple-testing problem. Patients who suffer rare adverse events may not be represented in small clinical trials. Treatment-responsive subgroups may comprise only a minority of patients grouped by current diagnostic categories. Such problems can be overcome with large sample sizes, but these can be expensive to collect and study. The STAR*D, CATIE, and STEP*BD projects were the first to provide samples large enough for genome-wide searches. Each of these studies collected a large group of patients with a common diagnosis (major depression, schizophrenia, and bipolar disorder, respectively) and assessed outcomes prospectively after relatively standardized treatment with one or more established psychotropic agents. These studies were not designed as pharmacogenetic studies but did collect DNA on many participants, thus enabling later pharmacogenetic studies that would not have otherwise been possible. We now need additional large samples. One approach might be to aggregate samples from the large numbers of ongoing clinical trials, as discussed further below.

Clinical and Genetic Sources of Heterogeneity

Even the most valuable pharmacogenetic markers never tell the whole story. Treatment outcomes are always the result of a complex interplay of individual, social, and stochastic factors. In psychiatry, adherence is a serious and often overlooked problem. For complex disorders, the best treatment would be one that uniquely corrects a specific molecular defect. This is being achieved for occasional patients with rare diseases, such as dopa-responsive dystonia (Bainbridge et al., 2011), but remains a major challenge, especially for neuropsychiatry.

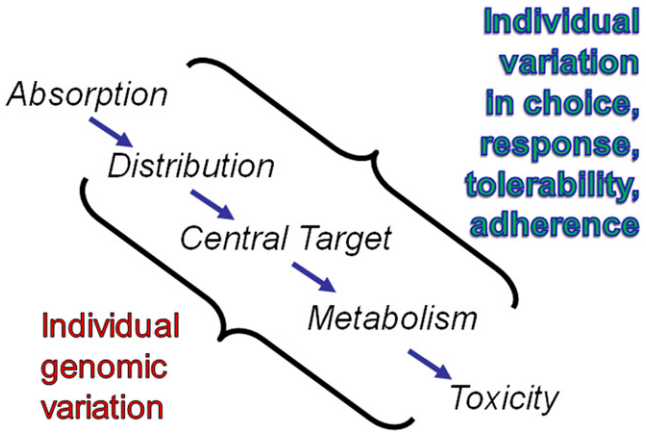

Figure 2. Approaches to the Pharmacogenomics of Psychotropic Medications
Individual variation reflects both genetic and nongenetic factors that converge on the absorption, distribution, central target, metabolism, and toxicity of medications.

Demonstrating Clinical Utility

The initial discovery phases of pharmacogenetic studies typically emphasize statistical significance and replication. These yardsticks are necessary for establishing the scientific reliability of a finding but tell us nothing about how valuable the information is for clinical decision making. Here, the well-established concept of "Number Needed to Screen" is valuable, because it incorporates both the frequency of a marker and the magnitude of its effect (Rembold, 1998). The NNS captures how many patients need to receive a test for every patient whose outcome is altered. Smaller NNS values are generally better, but there is no single threshold. If the goal is to avoid a severe adverse event, larger NNS might be reasonable, while quantitative improvements in response might require smaller NNS values to make sense clinically.

Physician Education

The interpretation of genetic information is a new challenge for most physicians. Because the clinical utility of pharmacogenetic markers typically is probabilistic, increasing the odds of one outcome versus another, it is not always clear how best to use this information in clinical decision making (Khoury et al., 2010). As genetic information becomes more comprehensive, the competing odds become more difficult to judge. This will require a kind of actuarial decision making that is unfamiliar to many clinicians. Medical school curricula are becoming more genetically informed, but reaching residents and practicing physicians in ways that can alter their clinical practice is challenging (Winner et al., 2010).

Conclusion: Some Paths Forward

Ultimately, better medications will follow from a better understanding of the biology of psychiatric disorders. This may take years, but there are several steps that can be taken now to make better use of what we already know and to position the field to capitalize quickly on new biologic insights, whenever they arise.

DNA Collection in Clinical Trials

We have already explained why genetic discoveries require large samples, but these can be slow and expensive to collect. Volunteers in ongoing clinical trials offer an attractive alternative. Although they represent a heterogeneous group in terms of ascertainment, diagnosis, and treatments employed, the many ongoing clinical trials may collectively constitute a reasonably representative sample of the population, well-suited to large-scale genetic studies. We need a coordinated effort by academia, industry, and government to begin collecting DNA in clinical trials and to send the samples and associated data—in anonymous form—to a central repository, where they can be used to fuel future large-scale studies.

Revisiting Underused Drugs that May Be Safe and Effective in Particular Groups

The pharmacopeia is full of drugs that seem to have outlived their usefulness or never found wide application: long-used medications known to be safe that have been superseded by drugs that are considered more efficacious; newer drugs that, while highly effective, were found to cause severe adverse events in some people. By use of genetic methods, it may be possible to "repurpose" some of these medications for other indications. If good genetic markers of safety and efficacy can be established, such repurposed drugs could be helpful for targeted populations, in which acceptable risk:benefit ratios can be more easily achieved. Systematic efforts along these lines are now being initiated in the National Center for Advancing Translational Sciences (NCATS). NCATS is a new component of the NIH that aims to catalyze the generation of innovative methods and technologies to enhance the development, testing, and implementation of diagnostic tests and therapeutic agents across a wide range of human ills (http://www.ncats.nih.gov).

Pharmacogenomics for Identifying New Drug Targets

Traditional drug development pipelines are inefficient and expensive. Innovative strategies are needed, but innovation requires new perspectives. Genetics is providing some of these new perspectives. Genome-wide association studies have revealed a spectrum of common genetic markers for a number of traits, diseases, and treatment outcomes. At about the same time, a whole new class of genetic variation was discovered, known as copy number variants (CNVs): deletions and insertions of small chromosomal segments, containing from one to dozens of genes. CNVs have been shown to play a major role in autism, schizophrenia, and developmental disorders and may also contribute to treatment outcomes (for review, see Malhotra and Sebat, 2012). CNVs often arise de novo as chromosomes are passed from parent to offspring, providing a dynamic source of genetic differences within every generation.

Large-scale sequencing of the genome is providing another new perspective. Thanks to this new technology, we now know that the average person harbors about 10,000 mutations that directly affect protein expression or structure, some 200 of which amount to total gene "knockouts" (MacArthur et al., 2012). We can only speculate how big a role such dramatic variation will play in future pharmacogenomics findings—but it will probably be large.

Genetics is not the whole answer but offers a solid starting point. Further knowledge of the basic disease processes at the cellular and molecular level will be required to discover ideal, curative treatments for most patients with neuropsychiatric disorders, but much could be achieved by personalizing the existing pharmacopeia. Personalized medicine will bring new insights, more treatment options, and better outcomes to what psychiatrists have always strived for—caring for each patient as an individual.

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